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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,381	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20051128; 20061219*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The amendment and election with traverse filed January 14, 2008, is acknowledged and has been entered. Claims 2-5, 7-30, and 33 have been canceled.

Applicant has elected the invention of Group I, claims 1, 6, and 32, drawn to a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 or a variant thereof, a nucleic acid molecule encoding said polypeptide or variant, a method of producing said polypeptide or variant, and a composition comprising said polypeptide or nucleic acid molecule.

2. The supplemental amendment and response filed February 11, 2008, is acknowledged and has been entered. Claims 6 and 31 have been amended.

3. Claims 1, 6, 31, and 32 are pending in the application and are currently under prosecution.

Election/Restrictions

4. Applicant's arguments traversing the propriety of the restriction and election requirement set forth in the Office action mailed December 12, 2007, are acknowledged.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the polypeptides of SEQ ID NO: 4 and SEQ ID NO: 6 share "a special technical feature" that distinguishes them over the prior art.

In response, as defined by PCT Rule 13.2, the expression "special technical feature" shall mean "those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art".

The inventions, which were restricted, are polypeptides comprising different amino acid sequences. Thus, the special technical feature of the inventions is making and/or using these different polypeptides.

Notably, M.P.E.P. § 1850 [R-2] states "lack of unity may exist within a single claim". § 1850 [R-2] further states:

> The situation involving the so-called Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by PCT Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in PCT Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

Defining "alternatives of a similar nature", § 1850 [R-2] states the alternatives within a single claim must have (a) a common property or activity and (b) a common substantial structure or in the absence of a common substantial structure, belong to a recognized class of chemical compounds, "mean[ing] that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention".

In this instance, because the polypeptides have different structures, and moreover, because the polypeptides need not have any common particularly identifying function that is attributable to any one common particularly identifying structural feature, it is not evident that the inventions are so related.

M.P.E.P. § 803.02 states:

> [I]t is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Again, since the polypeptides of the Markush group recited in claim 1, for example, do not necessarily share any one common *prima facie* utility, and because their structures differ, it is proper to restrict the subject matter encompassed by the claims into different groups of inventions.

Accordingly, the restriction and election requirement set forth in the Office action mailed December 12, 2007, is deemed proper and therefore made FINAL.

Information Disclosure Statement

5. The information disclosures filed November 28, 2005, and December 19, 2006, have been considered. An initialed copy of each is enclosed.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Notably, 37 C.F.R. § 1.52(c)(1) states, "[a]ny interlineation, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying oath or declaration pursuant to § 1.63 referring to those application papers and should be dated and initialed or signed by the applicant on the same sheet of paper" (underlining added for emphasis). Inasmuch as § 1.52(c)(1) makes separate reference to the oath or declaration it is believed clear that the rule does not apply to the oath or declaration but rather only to other application papers filed. Nonetheless, M.P.E.P. § 605.04(a) states, "Any changes made in ink in the application or oath prior to signing should be initialed and dated by the applicants prior to execution of the oath or declaration. The Office will not consider whether noninitialed and/or nondated alterations were made before or after signing of the oath or declaration **but will require a new oath or declaration**" (emboldened for emphasis).

Accordingly, a new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Priority

7. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of PCT Application No. PCT/JP03/12074, filed September 22, 2003, which claims benefit of U.S. Provisional Application No. 60/414,873, filed September 30, 2002, is acknowledged.

However, claims 1, 6, 31, and 32 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

In addition, it is aptly noted that claims 1, 6, 31, and 32 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of U.S. Provisional Application No. 60/414,873 because that application does not describe the claimed invention (i.e., it does not describe a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, or a nucleic acid molecule encoding such a polypeptide).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely November 28, 2005.

Drawings

8. The drawing set forth as Figure 1C is objected to because the figure depicts an amino acid sequence, which is not identified by a sequence identification number, either

in the figure or in the brief description of figure at page 9. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figure at page 4 of the specification to include sequence identification numbers.

Specification

9. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 1C are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 4.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an

amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

10. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks appearing in the specification include GenBank™ (see, e.g., page 5, line 28) and BiaCore™ (see, e.g., page 37, line 6).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

11. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appearing in this application are found in the specification at paragraphs [0114] and [0115] of the published application[1].

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See M.P.E.P. §

[1] U.S. Patent Application Publication No. 2006/0160991 A1.

608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

Claim Objections

12. Claims 1, 6, 31, and 32 are objected to as being directed in the alternative to the subject matter of a non-elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 6, 31,and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims are vague and indefinite because claims 1 and 31 recite, "that hybridizes under stringent conditions", where those conditions are not specified. Accordingly, the claim fails to define those particular conditions that are necessarily used to determine if any given nucleic acid molecule infringes the claim. Hybridization will or will not occur, or will occur to varying extents, depending upon the conditions under which a candidate nucleic acid molecule and a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3 are contacted. Under conditions that are relatively less "stringent", hybrid formation occurs more promiscuously, such that a nucleic acid molecule comprising a nucleotide sequence that is only partially identical to the complement of at least a portion of the nucleotide sequence of SEQ ID NO: 3 might anneal (pair) with a nucleic acid molecule comprising SEQ ID NO: 3; however, under conditions that are relatively more stringent, the candidate nucleic acid might not anneal with a nucleic acid molecule comprising SEQ ID NO: 3 unless it comprises a nucleotide

sequence that is fully complementary to at least a portion of SEQ ID NO: 3. Therefore, the hybridizing conditions effectively define the subject matter that is encompassed by the claim, thereby delineating the metes and bounds of the invention.

At paragraph [0049] of the published application, the specification describes different, exemplary "low" and "high" stringent hybridization conditions that might be used to define the nucleic acids that are considered members of the genus of "nucleic acids" to which the claims are directed. In light of this disclosure, it is apparent the subject matter encompassed by the claims might vary substantially, depending upon the hybridization conditions that are utilized to identify that subject matter. Furthermore, it appears that the specification does not provide a standard for ascertaining the requisite degree of stringency that must be used in identifying the claimed invention. Accordingly, since the "hybridizing conditions" used may vary, such that those conditions might be highly permissive (e.g., conditions under which even very dissimilar nucleic acid molecules remain hybridized) or highly selective (e.g., conditions under which only fully complementary nucleic acid molecules remain hybridized), the metes and bounds of the subject matter that Applicant regards as the invention will vary.

For these reasons, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite particularity and clarity to permit the artisan to known or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph.

(b) Claims 31 and 32 are indefinite because claim 31 recites the phrase "a pharmaceutically effective amount". The metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, where the claims recite the phrase "effective amount", yet fail to state the function that is necessarily achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). In this instance, it is apparent the amount must be *therapeutic or prophylactic*, so as to achieve the objective of its intended for use; however, the recitation that the effective amount be therapeutic or prophylactic does not obviate the basis of this rejection since it is still unclear what function (activity) the polypeptide or nucleic acid molecule is required to have when administered to a subject (e.g., a patient). Furthermore, it is unclear what

"pharmaceutical" effect the claims require the "effective amounts" of the active ingredients (i.e., the polypeptide or nucleic acid molecule) to be sufficient to achieve. The various endpoints and extents that define effective treatment and prevention are of a more conditional or qualitative nature. So, while the effective amounts of the active ingredients is required to be effective to *treat or prevent* a cancer in a subject, it is still not immediately evident what effect is necessarily achieved? It is submitted that the expected or desired effect that is to be achieved in the practice of the claimed invention to treat cancer, unless more particularly defined, is highly subjective and would tend to vary substantially; and accordingly, the claims fail to delineate with the requisite clarity and particularity the metes and bounds of the invention, so as to permit the skilled artisan to know or determine infringing subject matter.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 6, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001' hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims are directed to a genus of structurally and functionally disparate polypeptides and nucleic acid molecules encoding those polypeptides.

Although this genus includes the particularly described species of polypeptide that comprise the amino acid sequence of SEQ ID NO: 4, the claims are not so limited, and instead encompass any polypeptide in which one or more amino acids of the amino acid sequence of SEQ ID NO: 4 have been substituted by any other amino acid, in which one or more amino acids have been deleted, in which one or more amino acids have been inserted, and/or in which one or more amino acids have been added. As such, the claimed genus includes all polypeptides, which have "a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 4. Then, because the protein consisting of the amino acid sequence of SEQ ID NO: 4 has any of a large plurality of different biological activities (e.g., the ability to act as a substrate for one or more sequence dependent and sequence independent proteases), the claimed genus includes virtually any and all polypeptides.

In marked contrast to the breadth of the claims, it is submitted that the specification only provides an adequate description of the polypeptide of SEQ ID NO: 4 because it fails to describe with clarity and particularity the structural and functional features of at least a substantial number of the members of the claimed genus of structural and/or functional "variants" of the polypeptide of SEQ ID NO: 4, which would permit the skilled artisan to immediately envision, recognize, or distinguish those polypeptides.

Considering the extent to which the structures and/or functions of members of the claimed genus of polypeptides may vary, it is apparent that the polypeptide of SEQ ID NO: 4 cannot fairly be regarded as reasonably descriptive or representative of the claimed genus, as a whole.

Furthermore, although not limited to variants of the polypeptide of SEQ ID NO: 4, which might be produced by amino acid substitutions alone, the specification fails to describe which amino acids of the amino acids sequence set forth as SEQ ID NO: 4 can be replaced, and by which other amino acids, such that a resultant variant retains the structural and functional characteristics of the polypeptide of SEQ ID NO: 4, which

would permit the variant to be used in the same manner as the polypeptide of SEQ ID NO: 4.

Applicant is reminded that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 4 is capable of functioning the same, or even as having the same structure as the polypeptide of SEQ ID NO: 4.

Applicant is further reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes with the requisite clarity and particularity at least a substantial number of polypeptides, which are regarded as the invention.

Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying

characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of polypeptides, which vary both structurally and functionally, and the nucleic acid molecules encoding those polypeptides, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Finally, as to the intended use of the claimed composition comprising members of this genus of polypeptides, or the nucleic acid molecules encoding these polypeptides, while the specification asserts that the composition is useful to treat or prevent a cancer, there is no factual evidence of record that would support such an assertion.

The Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, e.g., the ability to inhibit the growth of a cancer, so as to achieve therapeutic effect, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the

genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a composition comprising a polypeptide or a nucleic acid molecule encoding a polypeptide that may be formulated as a pharmaceutical and administered to a subject afflicted with, or at risk of developing a cancer so as to achieve therapeutic effect; without such a composition, it is impossible to practice the invention.

Although the skilled artisan could potentially identify polypeptides that might be used to achieve therapeutic or prophylactic effect in treating or preventing cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

For all of the above reasons the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

17. Claims 1, 6, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, an isolated nucleic acid molecule comprising a nucleotide sequence encoding said polypeptide, an isolated vector comprising said nucleotide sequence encoding said polypeptide, an isolated host cell comprising said vector, and a method for making said polypeptide, said method comprising culturing said host cell, **does not reasonably provide enablement for making or using** the claimed inventions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the written description rejection above, the claims are directed to a genus of polypeptides that have no particular structure or function.

Accordingly, with the notable exception of the polypeptide of SEQ ID NO: 4, the specification would not reasonably enable the skilled artisan to either make or use a substantial number of members of the claimed genus.

One cannot make what has not been described; and one cannot use what cannot be made.

Furthermore, although many polypeptides can be made, not all polypeptides can be used in the manner in which the specification asserts.

This position is supported by the teachings of Skolnick et al. (*supra*), for example.

Then, inasmuch as claims 31 and 32 are directed to a composition that is to be used to prevent a cancer, it is aptly noted that the prevention of cancer is an intractable proposition, if not now wholly impractical, given, for example, that it is a heterogeneous disease, having widely varying pathologies and etiologies, and that its causes are multifactorial and as yet only partially characterized and poorly understood. It is generally recognized that a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development. As such, the specification, which lacks guidance, direction, and exemplification that is reasonably commensurate in scope with the breadth of the claims, would not reasonably enable the artisan to use the claimed invention to prevent cancer.

As claims 31 and 32 are specifically directed to pharmaceutical compositions comprising nucleic acid molecules encoding a polypeptide, it is apparent that the purported usefulness of the composition involves the use of the invention in processes termed in the art as "gene therapy".

The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without undue experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

Even were the claims limited to compositions comprising a polypeptide, as opposed to a nucleic acid molecule encoding that a polypeptide, there are still additional

reasons the specification would still not be reasonably enabling of the intended use of the claimed invention.

The use of the claimed invention has not been exemplified; and it is well known that the art of drug discovery is highly unpredictable.

With particular regard to anticancer drug discovery, Gura (*Science*. 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been

very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Bergers et al. (*Current Opinion in Genetics and Development.* 2000; **10**: 120-127) comments upon the inability to extrapolate preclinical data to reliably predict the outcome of treating humans using drugs tested in mice, particularly matrix metalloproteinase inhibitors. Bergers et al. teaches:

> A body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For

example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2).

In fact, Bergers et al. discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, paragraph bridging columns 1 and 2). Thus, the skilled artisan cannot accurately and reliably predict the effect of administering a pharmaceutical composition comprising an agent, such as the polypeptide of SEQ ID NO: 4, which is purported but not shown to have any desired pharmacological effect upon a disease, such as cancer, in a subject. Always the therapeutic effectiveness or efficacy of any unproven drug regimen can only be determined empirically.

Finally, it is noted that the claimed composition, which is intended for use in treating or preventing cancer, comprises a "variant" of the polypeptide of SEQ ID NO: 4, which has a biological activity equivalent to the polypeptide. Which biological activity of the polypeptide is necessarily retained by a variant of the polypeptide, such that the variant may be used to treat or prevent a cancer when administered to a subject in the form of the claimed composition? The specification fails to provide guidance or direction that would reasonably enable the artisan to know, but certainly it is not just any biological activity of the polypeptide of SEQ ID NO: 4 or a variant thereof, as the active ingredient, that might account for the purported usefulness of the claimed composition.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1, 6, 31, and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Ashida et al. (Database UNIPROT, Accession No. Q5KTR4, 15 February 2005)[2].

Ashida et al. teaches a polypeptide comprising the amino acid sequence of SEQ ID NO: 4; see entire document. Ashida et al. teaches a nucleic acid molecule comprising a nucleotide sequence encoding this polypeptide (i.e., EMBL Accession No. AB110785); see the annotations.

Although Ashida et al. does not expressly describe a polypeptide or nucleic acid molecule that is comprised within a composition comprising a pharmaceutically acceptable carrier (e.g., water), the nucleic acid molecule, for example, was necessarily comprised within such a composition at the time its nucleotide sequence was determined.

Furthermore, although Ashida et al. does not expressly describe a vector comprising the polynucleotide encoding the disclosed polypeptide, because the nucleotide sequence of the polynucleotide was determined, the polynucleotide was necessarily incorporated into a vector.

19. Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog (No. 1034 731/1006 924), page 93.

[2] See http://www.pir.uniprot.org/cgi-bin/upEntry?id=Q5KTR4_HUMAN.

Claim 31 is drawn to a composition comprising a nucleic acid comprising a nucleotide sequence encoding a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 and a pharmaceutically acceptable carrier (e.g., water).

The Boehringer Mannheim catalog teaches a kit comprising a collection of random primers. The collection comprises a multitude of isolated and purified nucleic acid molecules (i.e., primers), each of which consists of 6 nucleotide residues. The collection comprises nucleic acid molecules having every possible 6-nucleotide sequence of the four different nucleotide residues (i.e., A, C, T, and G) of which DNA is comprised. Therefore, the kit comprises a composition comprising a nucleic acid molecule consisting of a polynucleotide sequence encoding a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 4.

Although the nucleic acid molecule that is provided is a lyophilized solid, it was formally in solution; moreover, it cannot be used as intended without dissolution in an appropriate solution (e.g., a composition comprising water).

Conclusion

20. No claim is allowed.

21. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Database UNIPROT Accession No. Q7Z3A8 (01 May 1999)[3] teaches a polypeptide and a nucleic acid molecule encompassed by the present claims.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

[3] See http://www.pir.uniprot.org/cgi-bin/upEntry?id=MICA2_HUMAN.

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
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Primary Examiner, Art Unit 1643

slr
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